**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| IN RE APPLICATION OF: | SUBRAMANIAN *ET AL.* | EXAMINER: | MAEWALL, S. |
| APPLICATION NO.: | 10/777,415 | ART UNIT: | 1615 |
| FILED: | FEBRUARY 11, 2004 | CONF. NO: | 4311 |

FOR: **METHODS AND DOSAGE FORMS WITH MODIFIED VISCOSITY LAYERS**

# APPELLANT'S BRIEF ON APPEAL

Commissioner for Patents
Mail Stop Appeal Brief - Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The present paper is Appellant's Appeal Brief submitted in compliance with 37 C.F.R. §41.37(c) in response to the Final Rejection mailed April 25, 2008 and subsequent to a Notice of Appeal filed July 25, 2008. This Brief is accompanied by the fee set forth in 37 C.F.R. §41.20(b)(2).

## REAL PARTY IN INTEREST

The real party in interest is ALZA Corporation.

## RELATED APPEALS AND INTERFERENCES

Appellants are not aware of other appeals or interferences that would directly affect, be directly affected by, or have a bearing on the Board's decision in the present appeal.

## STATUS OF CLAIMS

The application as originally filed presented claims 1-39. Claims 5-27 and 30-39 were cancelled as drawn to a non-elected invention. Claims 1-4, 28, and 29 are pending and are the subject of the present Appeal. A listing of the claims as presently pending is set forth in Appendix A.

## STATUS OF AMENDMENTS

Appellants' amendment dated July 25, 2008 and filed subsequent to the final rejection dated April 25, 2008 was entered for purposes of appeal, as indicated in the Advisory Action dated September 5, 2008.

## SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter relates to a dosage form, as best depicted in Fig. 13. With reference to the numerical identifiers in Fig. 13, the dosage form as claimed includes:

(a) a membrane defining a compartment, the membrane having an exit orifice (Fig 13, 60) formed or formable therein and at least a portion of the membrane being semipermeable (¶¶ [00029], [00043]);

(b) an expandable layer (Fig 13, 50) located within the compartment remote from the exit orifice (Fig 13, 60) and in fluid communication with the semipermeable portion of the membrane (¶¶ [00029], [00043]);

(c) a delay layer (Fig 13, 30) located adjacent the exit orifice (¶¶ [00029], [00043])

(d) a drug layer (Fig 13, 40) located within the compartment between the delay layer (30) and the expandable layer (Fig 13, 50) (¶¶ [00029], [00043]); and

(e) an interface boundary between the delay layer (Fig 13, 30) and the drug layer (Fig 13, 40), the interface boundary being convex in shape relative to the exit orifice (¶¶ [00124], [00125]).

Feature (e), *i.e.*, a convex-shaped interface boundary between the delay layer and the drug layer, provides unexpected advantages over conventional dosage forms. In particular, the convex-shaped interface boundary reduces premature tunneling of the drug layer through the delay layer (*e.g.*, ¶ [00024]), resulting in greater uniformity in drug release/delivery and a more predictable delay period (*e.g.*, ¶ [00043]). These advantages are demonstrated by an exemplary dosage form (*e.g.*, ¶¶ [000124]-[000127] and Figs. 15 and 16).

## GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection for review on Appeal are:

1. Are claims 1-4, 28, and 29 obvious under 35 U.S.C. § 103 over Ayer *et al.* (WO 99/62496) in view of Jao *et al.* (U.S. Patent No. 5,252,338) and further in view of

Eckenhoff *et al.* (U.S. Patent No. 4,717,566) and Theeuwes (U.S. Patent No. 4,111,202)?

2. Are claims 28 and 29 obvious under 35 U.S.C. § 103 over Ayer *et al.* in view of Jao *et al.* and further in view of Eckenhoff *et al.* and Theeuwes and the Physician's Desk Reference?

## ARGUMENT

### A. Summary of Appellant's Arguments with Respect to both Grounds of Rejection

Appellants submit that the obviousness rejections are in error because none of the cited references, individually or in combination, describe or suggest the claimed dosage form. In particular, none of the cited references, nor their combination, describe or suggest a dosage form wherein the interface boundary between the delay layer and the drug layer is convex in shape relative to the exit orifice in the dosage form.

### B. Brief Summary of the Cited References

AYER *ET AL.* (WO 99162496) describe an oral dosage form that releases drug within a gastrointestinal tract at an ascending release rate over an extended period of time (page 6, lines 13-20; page 7, lines 1-3). In the tri-layer oral osmotic dosage form, a tablet core is surrounded by a semipermeable membrane that has an exit for releasing the drug formulation through the membrane (page 7, lines 6-17). The tablet core has a first drug-containing layer, a second drug containing layer and a third push layer (page 7, line 26 - page 8, line 2).

JAO *ET AL.* (U.S. Patent No. 5,252,338) describe a dosage form having a compartment having a drug composition and an osmotic composition. The wall surrounding the compartment comprises chemical means for slowing the rate of fluid imbibitions through the wall into the compartment (col. 4, lines 59-61). The drug composition comprises the drug and polymeric means for delaying the delivery of drug (col. 4, lines 4-6). Further, the compartment may include a layer positioned between the wall and the compositions in the inner compartment (21 in Fig. 3). This layer comprises a polymer to slow or delay the rate of fluid imbibition into the compartment (col. 5, lines 2-5).

ECKENHOFF *ET AL.* (U.S. Patent No. 4,717,566) describe a dosage form designed for retention in the ruminant of an animal. The dosage form includes a thermoresponsive drug layer, an expandable layer, and a dense layer. The dense layer (element 20 in Figs. 2-8) is

prepared from materials having a density of from about 0.8-82, such as iron, iron shot, stainless steel, copper oxide (col. 12, lines 44-65). The dense member can be "machined or cast as a single, solid piece made of stainless steel .... having a curved shape that corresponds to the internal shape of' the dosage form (col. 12, lines 57-61).

THEEUWES (U.S. Patent No. 4,111,202) describes a dosage form having two compartments (elements 13, 14 in Figs. 1B-1E and Figs. 2-3) separated by a film or membrane (element 18 in Figs. 1B-1E and Figs. 2-3; Col. 5, lines 27-35).

THE PHYSICIAN'S DESK REFERENCE lists cyclobenzaprine HCl.

C. Contentions of Appellants

C1. First Ground of Rejection: Claims 1-4 and 28-29

In maintaining the obviousness rejection, the Examiner looks to Ayer *et al.*'s teaching of two to three drug layers in a dosage form, asserts it would be obvious to modify one of the drug layers to a delay layer based on Jao *et al.*'s teaching of a delay layer in a dosage form, and that it would be obvious to make the interface between the drug layer and the delay layer convex based on Eckenhoff *et al.*'s and Theeuwes' showing of convex shapes in the drawings.

Appellants submit, and will show, that an informed consideration of the factors stated in *Graham v. John Deere* (383 U.S. 1, 148 USPQ 459 (1966)) leads to the conclusion that the claimed dosage form is not obvious in view of the cited references.

With respect to the first factor, scope and content of the asserted art, Ayer *et al.* and Jao *et al.* describe osmotic dosage forms that include an osmotic "push layer" adjacent a drug layer. The dosage form of Jao *et al.* includes, in the embodiment shown in Fig. 3, a delay layer (21) that surrounds the drug layer (16) and the osmotic push layer (18). Eckenhoff *et al.* describe a dosage form with a push layer (element 18 in Figs. 1-8), a drug layer (element 16 in Figs. 1-8), and a dense member (element 20 in Figs. 1-8) that serves to keep the dosage form in the rumen of an animal (Col. 5, lines 16-18). Theeuwes describes a dosage form having two compartments 13, 14 separated by a film or membrane 18 (col. 5, lines 27-35). Film 18 in Theeuwes when under pressure by an osmagent in compartment 14 is displaced, and as seen in Figs. 1C-1F will be convex in shape.

With respect to the second factor, differences between claimed subject matter and the asserted art, Appellants note that none of the cited art shows a dosage form wherein the interface boundary between the delay layer and the drug layer is convex in shape relative to

the exit orifice in the dosage form. To provide this element, the rejection relies on the drawings in Eckenhoff *et al.* and in Theeuwes, which show, a convex interface between a dense member (20) and a push layer (18) (Eckenhoff *et al.*), between a push layer (18) and a drug layer (16) (Eckenhoff *et al.*), or between a flexible film and a push layer (Theeuwes).

With respect to the third factor, the level of ordinary skill in the art, the question at hand is whether a person of ordinary skill in the art would, based on these combined teachings, modify Ayer *et al.* to include the delay layer of Jao *et al.*, and then further modify these combined teaches to have a convex interface between a drug layer and delay layer based on Eckenhoff *et al.* and Theeuwes, which illustrate a convex interface between layers in a dosage form, but not between a drug layer and a delay layer. In this analysis, the cited references must be viewed without the benefit of hindsight afforded by the claimed subject matter or accompanying specification.

In Eckenhoff *et al.*, convex-shaped layers 18, 20 are illustrated in some of the drawings (*i.e.*, Figs. 1-5, 7, and 8). However, a reading of Eckenhoff *et al.* reveals that neither of the convex shaped layers is a delay layer. Instead, convex layer 18 corresponds to an expandable member (or "push layer") of the dosage form (col. 9, line 48 - col. 10, line 18), and convex layer 20 corresponds to a dense member that has a high specific gravity to *prevent* the passage of the dosage form from the rumen (*e.g.*, col. 12, lines 36-65). Neither the expandable member 18 nor the dense member 20 is equivalent to a *delay layer*, nor is the interface between the expandable member 18 and the dense member 20 equivalent to an interface boundary between a delay layer and a drug layer. Nor would the expandable member 18 and the dense member 20 serve the equivalent function of a delay layer in a dosage form.

With respect to Theeuwes, the film or membrane 18 separates a first compartment 13 contains a beneficial agent/drug 16 (col. 5, lines 4-6) from a second compartment 14 that contains an osmagent 17 (*i.e.*, "push layer;" col. 5, lines 19-26). It is, therefore, apparent that film 18 is not equivalent to an interface boundary between a delay layer and a drug layer, nor would it serve the equivalent function in a dosage form.

It appears to be the Examiner's position that the fortuitous illustrations of a *convex shape* in Eckenhoff *et al.* and Theeuwes renders it obvious for a skilled artisan to apply the convex shape to an interface between layers in a dosage form, and in particular to an interface between a drug layer and a delay layer. Neither Eckenhoff *et al.* nor Theeuwes describe interfaces between layers, let alone a convex interface. Nor is there any mention of

any advantage to a convex interface between layers in a dosage form. Appellant asks the Board to carefully and mindfully question whether a skilled artisan would actually look at Eckenhoff *et al*. and Theeuwes and imagine taking a feature illustrated in the drawings, but not mentioned or discussed in the text, and applying that feature to a dosage form arrived at by combining Ayer *et al*. with Jao *et al*, and more specifically applying that illustrated feature to the drug/delay layers and not, for example to other layers, such as the push/drug layer. Absent the instant specification, Appellants simply fail to see the link to make these choices.

Moreover, the Supreme Court decision *KSR International Co. v. Teleflex Inc.,* S. Ct. 1727 (2007); 82 USPQ2d 1385, 1397 (2007), maintained that a still recognized test for nonobviousness of a claimed combination is whether the combination produces more than could be predicted from the prior art. Appellants direct the Board to paragraph [000125] in the application as filed, where it is noted that the claimed dosage form provides a more continuous and uniform ascending release profile than observed with dosage forms lacking the convex interface between the delay layer and the drug layer.

For at least the foregoing reasons, Appellants submit that the obviousness rejection is improper, and urge withdrawal of the rejection of claims 1-4 under 35 U.S.C. § 103.

C2. Second Ground of Rejection: Claims 28-29

The rejection of dependent claims 28-29 is a based on the combination of art discussed in C1 above (Ayer *et al*., Jao *et al*., Eckenhoff *et al*., and Theeuwes) in further combination with THE PHYSICIAN'S DESK REFERENCE for its listing of the drug recited in claims 28-29, cyclobenzaprine HCl.

In response, Appellants submit that the rejection of claims 28-29 cannot stand, for all the reasons noted in C1 above. Addition of the additional reference to the drug recited in claims 28-29 does not cure the deficiency in the rejection of claims 1-4. Withdrawal of the rejection of claims 28-29 is respectfully requested.

## CONCLUSION

In view of the foregoing, Appellants submit that the obviousness rejections are flawed and request the Board to reverse the rejections.

Respectfully submitted,

Date: September 25, 2008

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# CLAIMS APPENDIX

1. (Original) A dosage form comprising

(a) a membrane defining a compartment, the membrane having an exit orifice formed or formable therein and at least a portion of the membrane being semipermeable;

(b) an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semipermeable portion of the membrane;

(c) a delay layer located adjacent the exit orifice;

(d) a drug layer located within the compartment between the delay layer and the expandable layer; and

(e) an interface boundary between the delay layer and the drug layer, the interface boundary being convex in shape relative to the exit orifice.

2. (Original) The dosage form of Claim 1 wherein the delay layer and the drug layer are formed by a compression sequence in which the delay layer is compressed into its form prior to the drug layer being compressed into its form.

3. (Original) The dosage form of Claim 1 wherein:

the delay layer exhibits a higher viscosity than the drug layer when both are subjected to the same level of hydration.

4. (Original) The dosage form of Claim 1 wherein:

the viscosity of the delay layer is higher than the viscosity of the drug layer at equivalent aqueous saturation levels.

5-27. Cancelled

28. (Previously presented) The dosage form of Claim 1 wherein the drug layer comprises a drug selected from the group of cyclobenzaprine, amitriptyline, imipramine and desipramine.

29. (Original) The dosage form of Claim 1 wherein the drug layer comprises cyclobenzaprine and that provides a cyclobenzaprine plasma concentration of 6 to 8 ng/ml

three to four hours after dosing and approximately 8 to 12 ng/ml eighteen to twenty hours after oral administration in a human.

30-38. Cancelled

## EVIDENCE APPENDIX

None.

## Related Proceedings Appendix

None.